

RESEARCH MONOGRAPH . COMPOUND PROFILE

Vesugen

A Khavinson-class synthetic tripeptide bioregulator derived from vascular wall protein sequences, characterized by epigenetic modulation of endothelial proliferation markers, endothelin-1 normalization, sirtuin-1 upregulation, and neuroprotective gene regulation in preclinical aging and Alzheimer's disease models.

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ABSTRACT

Vesugen (Lys-Glu-Asp; KED) is a synthetic tripeptide bioregulator developed at the Saint Petersburg Institute of Bioregulation and Gerontology under the direction of Professor Vladimir Khavinson as part of a decades-long program investigating short-chain peptide regulation of age-associated tissue decline. The compound belongs to the Khavinson class of ultrashort (two to four amino acid residue) bioregulatory peptides, a family of synthetic sequences derived from organ-specific protein fractions that are proposed to penetrate cell nuclei and modulate gene expression through direct interactions with DNA promoter regions and epigenetic regulatory mechanisms. Vesugen is the synthetic analog corresponding to the vascular-wall-derived peptide fraction originally isolated as the active component of Ventfort, a polypeptide complex extracted from bovine aortic tissue. The tripeptide sequence Lys-Glu-Asp was identified as the minimal bioactive motif responsible for the vasoprotective activity of the parent extract.

The molecular pharmacology of Vesugen is characterized by epigenetic modulation of vascular endothelial cell function. In dissociated human endothelial cell cultures, Vesugen stimulates synthesis of the proliferation-associated protein Ki-67, the expression of which declines during cellular aging [1]. Molecular docking studies demonstrate that Vesugen binds to the promoter region of the MKI67 gene, making contact through the CATC sequence at the core promoter located between positions -14 and +12 relative to the transcription initiation site [1]. In models of atherosclerotic and restenotic endothelium in vitro, Vesugen

normalizes the expression of endothelin-1, restores connexin (Cx37, Cx43) expression for intercellular communication, and increases sirtuin-1 (SIRT1) expression, implicating the compound in DNA repair and cellular longevity pathways [2, 3]. The compound also modulates expression of vascular endothelial growth factor (VEGF) and the apoptosis marker p53, contributing to a net pro-proliferative and anti-apoptotic phenotype in aged vascular endothelial cells.

Beyond its primary vascular target, Vesugen has demonstrated neuroprotective activity in several preclinical models. The tripeptide regulates expression of cell aging and apoptosis genes (p16, p21), neuronal differentiation genes and proteins (NES, GAP43, nestin), and genes implicated in Alzheimer's disease pathogenesis (SUMO, APOE, IGF1) [4]. In hippocampal neuron cultures exposed to amyloid-beta synaptotoxicity, Vesugen increased the number of mushroom-type dendritic spines by 20 percent [5]. Oral administration of Vesugen improved memory and attention in elderly individuals with functional central nervous system disorders in a small clinical cohort [4]. In a 32-patient clinical study of elderly individuals with chronic polymorbidity and organic brain syndrome, Vesugen demonstrated anabolic properties and improved central nervous system activity, slowing the rate of aging as measured by biological age indicators [6].

The compound is not approved by any national regulatory authority as a pharmaceutical product. It is supplied as a research-grade synthetic peptide and as a dietary supplement (capsule form) in certain jurisdictions. The primary literature on Vesugen originates predominantly from Russian research institutions, principally the Saint Petersburg Institute of Bioregulation and

Gerontology and affiliated laboratories. Independent replication by Western laboratories using contemporary structural biology and pharmacology methodologies remains limited. This monograph reviews the chemistry, proposed mechanism of action, preclinical pharmacology, limited clinical evidence, sourcing and handling considerations, and a comparative assessment against five alternative vasoprotective and geroprotective peptide candidates.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Common name: Vesugen.

Peptide sequence designation: KED (single-letter amino acid code); Lys-Glu-Asp (three-letter amino acid code).

Full chemical name: L-lysyl-L-glutamyl-L-aspartic acid. The compound is the linear tripeptide of L-lysine, L-glutamic acid, and L-aspartic acid joined by standard alpha-peptide bonds.

Alternative designations: T-38 peptide (internal designation at the Saint Petersburg Institute of Bioregulation and Gerontology); Vezugen (transliteration variant from Russian); vascular peptide bioregulator KED.

Relationship to Ventfort: Vesugen is the synthetic tripeptide analog of the bioactive fraction of Ventfort, a polypeptide complex isolated from bovine aortic tissue. Ventfort (also designated the A-3 peptide complex) contains the native peptide mixture from which the Lys-Glu-Asp sequence was identified as the minimal vasoprotective motif [7, 8]. The two preparations are not interchangeable; Ventfort is a crude tissue extract containing multiple peptide species, while Vesugen is a defined synthetic tripeptide of known sequence and purity.

Chemical Abstracts Service registry number: Not assigned to the tripeptide under the name Vesugen in the CAS registry as of monograph preparation. The compound is catalogued by research suppliers under the peptide sequence designation Lys-Glu-Asp.

1.2 Structural class and chemistry

Vesugen belongs to the class of ultrashort bioregulatory peptides, defined by Khavinson and colleagues as synthetic peptides of two to four amino acid residues that regulate gene expression through direct interaction with DNA and chromatin components [9, 10]. The structural class is distinguished from conventional bioactive peptides (typically 5 to 50 residues) by the extremely short chain length, the ab-

sence of defined secondary structure in solution, and the proposed mechanism of action through nuclear translocation and DNA minor groove binding rather than through cell-surface receptor activation.

Molecular formula: C₁₅H₂₆N₄O₈ (zwitterionic form).

Molecular weight: 390.39 g/mol.

Physical properties: White to off-white amorphous or crystalline powder. Freely soluble in water and aqueous buffers at physiological pH. The compound carries a net charge that is pH-dependent: at physiological pH (7.4), the lysine side chain carries a positive charge, while the glutamic acid and aspartic acid side chains carry negative charges, yielding a net charge of approximately -1. The isoelectric point is approximately 3.9.

Stereochemistry: All three residues are in the L-configuration. The compound contains no stereocenters beyond the alpha-carbons of the constituent amino acids. Research-grade material should be confirmed as the all-L isomer by chiral chromatography or by enzymatic degradation with L-specific aminopeptidases.

1.3 Synthesis

The synthesis of Vesugen is straightforward by standard solid-phase peptide synthesis (SPPS) using Fmoc (9-fluorenylmethoxycarbonyl) chemistry. The three amino acids are coupled sequentially on a solid resin support (typically Wang resin or Rink amide resin for the C-terminal aspartic acid), with standard side-chain protecting groups (Boc for lysine, OtBu for glutamic acid and aspartic acid). Following assembly, the peptide is cleaved from the resin with trifluoroacetic acid cocktail, precipitated in cold diethyl ether, and purified by reverse-phase high-performance liquid chromatography (RP-HPLC). The final product is lyophilized to yield the trifluoroacetate salt or converted to the acetate salt by ion exchange. Yields are characteristically high (greater than 80 percent crude, greater than 95 percent after HPLC purification) owing to the short chain length and the absence of difficult coupling steps. The compound is also accessible by solution-phase synthesis using standard carbodiimide or active ester coupling chemistry, though SPPS is the preferred method for research-grade production.

Identity is confirmed by electrospray ionization mass spectrometry (expected [M+H]⁺ = 391.17), amino acid analysis, and RP-HPLC retention time comparison to a reference standard. Purity is assessed by analytical RP-HPLC (typically greater than

98 percent for research-grade material) and by residual solvent analysis.

2. Abstract

Vesugen (Lys-Glu-Asp; KED) is a synthetic tripeptide bioregulator of the Khavinson class, developed at the Saint Petersburg Institute of Bioregulation and Gerontology as the synthetic analog of the vasoprotective peptide fraction derived from bovine aortic tissue (Ventfort). The compound represents one member of a larger family of ultrashort (two to four residue) synthetic peptides proposed to regulate age-associated tissue decline through epigenetic modulation of gene expression via direct interactions with DNA promoter regions and chromatin components [9, 10].

The primary research interest in Vesugen centers on vascular endothelial cell biology and aging. In dissociated endothelial cell cultures from young and aged organisms, Vesugen stimulates the proliferation-associated protein Ki-67, normalizes endothelin-1 expression under atherosclerotic and restenotic conditions, restores connexin-mediated intercellular communication, and upregulates sirtuin-1 (SIRT1) expression [1, 2, 3]. The proposed mechanism involves nuclear translocation of the tripeptide and direct binding to the CATC motif in the core promoter region of the MKI67 gene, as demonstrated by molecular docking studies [1]. These findings position Vesugen as a candidate compound for investigation of peptide-mediated epigenetic regulation of vascular aging, though the binding model has not been independently verified by crystallographic or cryo-electron microscopy structural methods.

A secondary research application is neuroprotection. Vesugen modulates expression of neuronal differentiation markers (nestin, GAP43), cell cycle arrest genes (p16, p21), and Alzheimer's disease-associated genes (SUMO, APOE, IGF1) in cell culture models [4]. In hippocampal neurons exposed to amyloid-beta, Vesugen produced a modest (20 percent) increase in mushroom-type dendritic spines [5]. Oral Vesugen improved memory and attention in a small cohort of elderly individuals with functional central nervous system disorders [4].

Clinical evidence for Vesugen is limited to small cohort studies conducted at Russian research institutions. A 32-patient study in elderly individuals with chronic polymorbidity reported improved biological age markers and central nervous system activity following Vesugen treatment [6]. A 41-patient study of the related preparation Vezugen in patients with lower-limb chronic arterial insufficiency re-

ported significant improvement in arterial blood flow [11]. The Ventfort polypeptide complex (from which Vesugen was derived) was evaluated in a 49-patient clinical study in atherosclerosis and senile purpura, demonstrating reduction in total cholesterol and improvement in capillary wall strength [7].

The compound is not approved as a pharmaceutical by any regulatory authority. It is sold as a research-grade peptide and as a dietary supplement in capsule form. The evidence base is predominantly from the Khavinson laboratory and affiliated institutions; independent replication is limited. Investigators should approach efficacy claims with appropriate caution and should obtain independent analytical verification of identity and purity on every lot.

3. Discovery and Development History

3.1 Origin and the Khavinson peptide bioregulator program

The development of Vesugen is inseparable from the broader Khavinson peptide bioregulator research program, which originated in Soviet military medicine in the 1970s and 1980s. Professor Vladimir Khavinson, working at the Military Medical Academy in Leningrad (now Saint Petersburg), initiated a systematic program to isolate tissue-specific peptide fractions from animal organs and to characterize their effects on corresponding human tissues [12, 13]. The rationale was that short peptide sequences present in organ-specific protein extracts could serve as endogenous regulators of tissue homeostasis, and that their administration could restore declining tissue function in aging and disease.

Over approximately four decades, the program produced six registered pharmaceutical preparations (Timalin from thymus, Epithalamin from pineal gland, Prostatilen from prostate, Cortexin from cerebral cortex, Retinalamin from retina, and Thymogen as a synthetic dipeptide) and more than 60 dietary supplement formulations based on organ-specific peptide complexes [12, 13].

3.2 From Ventfort to Vesugen

The vascular peptide bioregulator program began with the isolation of a polypeptide complex from bovine aortic tissue, designated Ventfort (also referred to as the A-3 peptide complex). Ventfort was characterized as a mixture of short peptides with molecular weights below approximately 10 kDa, extracted by acid hydrolysis and size-exclusion chromatography from aortic wall homogenate. Clinical evaluation of Ventfort in 49 patients with arterial atherosclerosis and senile purpura (2003 to 2004, Saint Petersburg Institute of Bioregulation and Gerontology) demonstrated reduction in total blood cholesterol, decreased very-low-density lipoprotein content, and improvement in capillary wall strength as measured by the Hesse test [7].

The identification of the active tripeptide sequence followed the general Khavinson methodology: sequential fractionation of the polypeptide complex, activity-guided selection of the minimal sequence retaining biological activity in cell

culture assays, and chemical synthesis of the identified sequence. The tripeptide Lys-Glu-Asp (KED) was identified as the minimal vasoprotective motif and designated Vesugen [8]. The synthetic tripeptide was then characterized independently of the parent Ventfort extract in cell culture and in limited clinical studies.

3.3 Timeline of key publications

The published literature on Vesugen spans approximately 2012 to 2024. The Chalisova et al. (2012) report established the effect of tripeptide Lys-Glu-Asp on neuroimmunoendocrine system cell physiology [2]. The Khavinson, Tarnovskaya et al. (2014/2015) report characterized the epigenetic mechanism of Ki-67 gene regulation in vascular endothelial cells [1]. The Kraskovskaya et al. (2017) report demonstrated neuronal spine restoration under amyloid-beta challenge [5]. The Khavinson, Linkova, Umnov (2021) review consolidated the molecular-genetic aspects of KED in Alzheimer's disease neurogenesis regulation [4]. The Kraskovskaya, Linkova et al. (2024) report extended neuroprotective findings to fibroblast-derived induced neurons [14]. The Khavinson, Linkova, Dyatlova et al. (2022) review situated Vesugen within the broader context of senescence-associated secretory phenotype regulation in cardiovascular aging [3].

4. Mechanism of Action

4.1 Proposed epigenetic mechanism: DNA minor groove binding

The central mechanistic hypothesis for Vesugen and the broader Khavinson ultra-short peptide class is that these peptides penetrate the cell membrane, translocate to the nucleus, and interact directly with DNA in the minor groove of the double helix at specific promoter regions, thereby modulating transcription of target genes [9, 10]. This hypothesis was developed through a series of molecular modeling, molecular docking, and cell culture studies conducted primarily at the Saint Petersburg Institute of Bioregulation and Gerontology.

The Khavinson and Popovich (2021) systematic review of peptide regulation of gene expression consolidated the evidence for this mechanism across the ultra-short peptide class [10]. Short peptides of two to seven amino acid residues were demonstrated to penetrate cell nuclei and nucleoli, interact with nucleosomes and histone proteins, and bind both single-stranded and double-stranded DNA. The proposed interaction involves hydrogen bonding and electrostatic contacts between the peptide side chains and the DNA bases and phosphate backbone in the minor groove, with sequence selectivity conferred by the specific combination of charged and polar residues in the peptide.

For Vesugen specifically, molecular docking studies demonstrated binding to the promoter region of the MKI67 gene (encoding the proliferation marker Ki-67), with the peptide making contact through the CATC sequence motif in the core promoter region located between positions -14 and +12 relative to the transcription initiation site [1]. The binding is proposed to enhance transcription factor access and to increase MKI67 expression, thereby promoting endothelial cell proliferation in aged tissues where Ki-67 expression has declined.

It should be noted that this mechanistic model, while supported by computational docking and by correlative gene expression data, has not been independently validated by experimental structural biology methods such as X-ray crystallography, nuclear magnetic resonance spectroscopy, or cryo-electron microscopy of DNA-peptide complexes. The binding affinity, kinetics, and stoichiometry of the

proposed interaction have not been quantified by biophysical methods such as surface plasmon resonance or isothermal titration calorimetry. The mechanistic model should therefore be regarded as a working hypothesis supported by computational and correlative evidence rather than as an established molecular mechanism.

4.2 Vascular endothelial targets

The vascular pharmacology of Vesugen has been characterized in dissociated endothelial cell cultures under normal, atherosclerotic, and restenotic conditions. The following molecular targets have been identified:

Ki-67 (MKI67): Vesugen stimulates synthesis of the proliferation-associated protein Ki-67 in endothelial cell cultures from aged organisms, where Ki-67 expression is diminished relative to young controls [1]. The functional consequence is restoration of endothelial cell proliferative capacity, supporting renewal of the vascular intima and counteracting accumulation of senescent cells with pro-inflammatory and pro-thrombotic phenotypes.

Endothelin-1 (ET-1): In models of atherosclerotic and restenotic endothelium, Vesugen normalizes the elevated expression of endothelin-1, a potent vasoconstrictor peptide that is characteristically upregulated in endothelial dysfunction [2, 3]. The normalization of ET-1 expression is proposed to contribute to vasoprotection by reducing pathological vasoconstriction and endothelial activation.

Connexins (Cx37, Cx43): Vesugen restores connexin expression in aged and pathological endothelial cell cultures [2, 3]. Connexins form gap junction channels that mediate intercellular communication between endothelial cells and between endothelial and smooth muscle cells; their decline during aging contributes to impaired vascular coordination and is associated with atherosclerotic plaque progression.

Sirtuin-1 (SIRT1): Vesugen increases SIRT1 expression in endothelial cell cultures [2, 3]. SIRT1 is a NAD⁺-dependent deacetylase with established roles in DNA repair, chromatin remodeling, metabolic regulation, and cellular longevity. SIRT1 activation mimics some molecular effects of caloric restriction, a well-characterized longevity intervention. The upregulation of SIRT1 by Vesugen is proposed to contribute to vascular protection through enhanced DNA repair capacity and suppression of the senescence-associated secretory phenotype.

p53 and apoptosis markers: Vesugen modulates p53 expression in endothelial and neuroimmunoendocrine cell cultures, with the net effect of reducing apoptotic signaling and promoting cell survival in aged tissues [2].

Vascular endothelial growth factor (VEGF): Vesugen modulates VEGF expression, contributing to angiogenic signaling and endothelial maintenance [3].

4.3 Neuronal targets

The neuroprotective pharmacology of Vesugen extends beyond the primary vascular indication:

Neuronal differentiation markers: Vesugen regulates expression of NES (nestin) and GAP43 genes and their corresponding proteins, both markers of neuronal differentiation and plasticity [4]. Nestin is an intermediate filament protein expressed in neural progenitor cells; GAP43 (growth-associated protein 43) is a presynaptic phosphoprotein involved in axonal growth and synaptic plasticity.

Cell cycle arrest genes: Vesugen modulates expression of p16 (CDKN2A) and p21 (CDKN1A), cyclin-dependent kinase inhibitors that enforce cell cycle arrest during cellular senescence [4]. The direction and magnitude of modulation depend on cell type and experimental conditions.

Alzheimer's disease-associated genes: Vesugen regulates expression of SUMO (small ubiquitin-like modifier), APOE (apolipoprotein E), and IGF1 (insulin-like growth factor 1), all implicated in Alzheimer's disease pathogenesis [4]. The functional significance of these expression changes for disease modification has not been established in vivo.

Dendritic spine morphology: In hippocampal neuron cultures exposed to amyloid-beta synaptotoxicity, Vesugen at 200 ng/mL increased the number of mushroom-type dendritic spines by 20 percent [5]. Mushroom spines are the mature, stable spine morphology associated with functional synapses; their loss is a hallmark of amyloid-beta-driven synaptic degeneration in Alzheimer's disease models. The 20 percent restoration by Vesugen was modest compared to the 71 percent restoration achieved by the related tripeptide EDR (Glu-Asp-Arg) in the same study [5].

4.4 Anti-inflammatory and SASP modulation

Vesugen is positioned within a broader class of peptides that modulate the senescence-associated secretory phenotype (SASP) of cardiovascular cells. The Khavinson, Linkova, and Dyatlova (2022) review identified the KED tripeptide as one of several vasoprotective peptides that regulate molecules involved in inflammaging and SASP formation in cardiovascular system cells [3]. The SASP consists of pro-inflammatory cytokines (including TNF-alpha, IL-6, IL-1beta), matrix metalloproteinases, and growth factors secreted by senescent cells, and its accumulation drives chronic low-grade inflammation (inflammaging) that contributes to atherosclerosis, coronary heart disease, and myocardial infarction. The proposed mechanism of SASP modulation by Vesugen involves upregulation of SIRT1 (which suppresses NF-kappaB-driven inflammatory gene transcription) and normalization of endothelial cell proliferation to reduce the fraction of senescent cells in the vascular endothelium.

4.5 Limitations of the mechanistic evidence

Several important limitations constrain interpretation of the proposed mechanism of action:

First, the DNA minor groove binding model is based on computational molecular docking rather than experimental structural determination. The specificity and affinity of the proposed DNA-peptide interaction have not been quantified by independent biophysical methods.

Second, the majority of mechanistic studies originate from the Khavinson laboratory and affiliated institutions. Independent replication by laboratories outside the Russian peptide bioregulator research network is limited, though recent collaborative publications with Italian research groups (Avolio, Martinotti et al.) have begun to extend the evidence base [15].

Third, the causal relationship between the observed gene expression changes and the functional outcomes (vascular protection, neuroprotection, cognitive improvement) has not been established through genetic or pharmacological loss-of-function experiments (such as Ki-67 knockout, SIRT1 inhibition, or connexin blockade in the presence of Vesugen).

Fourth, the nuclear translocation of a tripeptide across both the plasma membrane and the nuclear envelope is thermodynamically plausible given the small molecular size (390 Da) but has not been directly visualized by fluorescent labeling or by autoradiography with radiolabeled Vesugen in intact cells.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

The pharmacokinetics of Vesugen in humans have not been characterized by formal pharmacokinetic studies with plasma concentration-time profiling. The compound is administered orally (capsule form in supplement preparations) and by subcutaneous injection (research-grade reconstituted peptide).

Oral bioavailability of tripeptides is generally low owing to proteolytic degradation by gastric and pancreatic proteases and by brush-border peptidases in the small intestine. However, the Khavinson laboratory has proposed that ultrashort peptides (two to four residues) may be absorbed intact through peptide transporter-mediated uptake (PepT1/SLC15A1 and PepT2/SLC15A2 transporters) and through paracellular absorption, with sufficient systemic exposure to achieve biological activity at target tissues [10, 16]. A 2022 publication examined the transport of biologically active ultrashort peptides using POT (proton-coupled oligopeptide transporter) and LAT (L-type amino acid transporter) carriers, providing evidence that di- and tripeptides of the Khavinson class can utilize these transport systems for intestinal absorption [16]. The extent of oral bioavailability for Vesugen specifically has not been quantified.

Sublingual administration has been explored as an alternative route to bypass gastrointestinal proteolysis. Vesugen Lingual is marketed as a sublingual formulation, though pharmacokinetic comparisons between oral and sublingual routes have not been published.

5.2 Distribution

No formal distribution studies have been reported. Given the molecular weight (390 Da) and the hydrophilic, charged nature of the peptide, extensive tissue distribution with limited protein binding is expected. The proposed mechanism of action

requires intracellular and intranuclear penetration, which the Khavinson group has proposed occurs through passive diffusion and/or active transport for peptides of this size class [9, 10].

5.3 Metabolism

Tripeptides are metabolized by ubiquitous intracellular and extracellular peptidases. The Lys-Glu-Asp sequence is susceptible to cleavage by aminopeptidases (at the Lys-Glu bond) and by carboxypeptidases (at the Asp C-terminus). Plasma half-life of an unprotected linear tripeptide is typically on the order of minutes. The Khavinson laboratory has proposed that the biological activity of ultrashort peptides may not require sustained plasma concentrations, as the epigenetic effects on gene expression may persist beyond the pharmacokinetic residence of the peptide itself (a "hit-and-run" or "trigger" mechanism) [10]. This hypothesis is consistent with the clinical dosing paradigm of short courses (10 to 15 days) followed by sustained clinical effects reported in Ventfort studies [7].

5.4 Elimination

No formal elimination studies have been reported. The constituent amino acids (lysine, glutamic acid, aspartic acid) are endogenous and are metabolized through standard amino acid catabolic pathways following peptide hydrolysis.

5.5 Routes of administration

Three routes are used in research and supplement applications:

Oral: Capsule form containing lyophilized Vesugen, typically 200 mcg per capsule. The most common supplement regimen is 1 to 2 capsules daily for 10 to 30 days.

Subcutaneous injection: Research-grade Vesugen reconstituted in bacteriostatic water for injection. Doses used in research settings are in the range of 10 to 100 mcg per injection.

Sublingual: Vesugen Lingual formulation for mucosal absorption, bypassing gastrointestinal proteolysis.

6. Preclinical Pharmacology

6.1 Vascular endothelial cell culture studies

The foundational preclinical evidence for Vesugen derives from in vitro studies in dissociated vascular endothelial cell cultures. Khavinson, Tarnovskaya et al. (2014) demonstrated that Vesugen stimulated Ki-67 expression in endothelial cell cultures from aged animals, while molecular docking confirmed binding to the MKI67 gene promoter [1]. Studies of Vesugen effect on signaling molecule expression in human embryonic endothelial cells examined the compound under normal, atherosclerotic, and restenotic conditions, demonstrating normalization of endothelin-1, restoration of connexin Cx37 and Cx43 expression, upregulation of SIRT1, and modulation of VEGF and p53 [2, 3].

6.2 Neuroimmunoendocrine system studies

Chalisova et al. (2012) characterized the effect of tripeptide Lys-Glu-Asp on organotypic cultures of neuroimmunoendocrine system cells from young and old animals [2]. The peptide stimulated proliferation and inhibited apoptosis, with effects more pronounced in cultures from old animals than from young animals. The proliferation marker Ki-67 was increased while the apoptosis marker p53 was decreased. Expression of immune markers CD5 (lymphocytes) and CD68 (macrophages) was induced, though less prominently in older cultures. Behavioral testing using honey bee associative learning models demonstrated that the tripeptide modulated both short-term and long-term memory formation.

6.3 Neuronal spine and dendritic morphology studies

Kraskovskaya et al. (2017) examined the effect of tripeptides on neuronal spine morphology under conditions of amyloid-beta synaptotoxicity in mouse hippocampal neuron cultures [5]. Vesugen (KED) at 200 ng/mL increased mushroom-type spines by 20 percent under amyloid challenge. The related tripeptide EDR (Glu-Asp-Arg) at the same concentration increased mushroom spines by 71 percent, restor-

ing spine counts to normal levels. The authors recommended EDR rather than KED for further Alzheimer's disease research on the basis of superior effect size, though both peptides demonstrated neuroprotective activity.

Kraskovskaya, Linkova et al. (2024) extended neuroprotective findings to fibroblast-derived induced neurons from aged donors [14]. EDR, KED, and AEDG (the Epitalon tetrapeptide) all enhanced dendritic growth by increasing both the number and length of neuronal branches. EDR specifically reduced oxidative DNA damage. The peptides showed no significant effect on mitochondrial activity, lysosomal function, or p16 protein levels.

6.4 Lipoprotein and lipid peroxidation studies

Vesugen has been reported to restrict lipid peroxidation of human lipoproteins by modifying their structure, suggesting an indirect antioxidant role relevant to atherosclerosis [3]. The compound does not possess direct radical-scavenging antioxidant activity (it lacks redox-active functional groups) but may reduce oxidative modification of low-density lipoproteins through conformational effects on the apolipoprotein or through upregulation of endogenous antioxidant enzyme expression via the SIRT1 pathway.

6.5 Animal studies

The Ventfort polypeptide complex (the parent preparation from which Vesugen was derived) has been studied in animal models of vascular aging and hypertension. Published reports describe effects on microcirculation in the brain cortex of old rats and in spontaneously hypertensive rats [8]. Long-term treatment with Khavinson peptide preparations, including vascular-targeted formulations, increased mean lifespan by 20 to 40 percent in rodent models and suppressed development of spontaneous and induced tumorigenesis [12]. However, it is important to note that these lifespan studies used the crude Ventfort polypeptide complex or multi-peptide regimens rather than isolated Vesugen tripeptide, and the specific contribution of the KED sequence to the observed effects cannot be isolated from these studies.

7. Clinical Evidence Base

7.1 Clinical studies with Vesugen

Meshchaninov et al. (2015): A study of 32 participants (18 men, 12 women; ages 41 to 83) with chronic polymorbidity and organic brain syndrome of the central nervous system in remission examined the effects of Vesugen and Pinealon (a separate tripeptide bioregulator) [6]. Both peptides demonstrated anabolic properties and improved central nervous system activity, slowing the rate of aging as assessed by biological age indicators. Vesugen showed more pronounced protective effects than Pinealon. Neither peptide affected chromatin condensation, indicating nuclear genetic safety at tested doses. Decreased CD34+ hematopoietic cell counts were observed, though the clinical significance of this finding was not established. The authors recommended both peptides as geroprotectors for patients with vascular or traumatic brain syndrome. This study was not randomized or placebo-controlled.

Kitachev et al. (2014): A study of 41 patients with chronic arterial insufficiency of the lower extremities examined the effect of Vezugen (Vesugen) monotherapy on penile artery blood flow as a measure of endothelial function [11]. Blood flow through the main penile artery improved significantly after Vesugen treatment by both clinical assessment and objective indicators. The investigation highlighted endothelial dysfunction as the primary pathological mechanism and attributed improvement to Vesugen's vasoprotective properties. This study was not randomized or placebo-controlled.

Khavinson, Linkova, Umnov (2021) review: This review consolidated evidence that oral application of KED improved memory and attention in elderly individuals with functional central nervous system disorders [4]. The primary data underlying this claim derive from the Meshchaninov et al. study and from unpublished or Russian-language-only clinical observations not available for independent verification.

7.2 Clinical studies with Ventfort (parent preparation)

Ventfort clinical study (2003-2004): A study at the Saint Petersburg Institute of Bioregulation and Gerontology evaluated Ventfort in 49 patients (27 treatment, 22 control) with arterial atherosclerosis and senile purpura, ages 52 to 84 [7]. The treatment group received Ventfort 1 to 2 capsules 2 to 3 times daily for 10 to 15 days. Results included improvement in general health (particularly in patients with cerebrovascular disorders), significant decrease in total blood cholesterol, tendency toward decreased very-low-density lipoprotein levels, increased capillary wall strength on Hesse testing, and decreased hemorrhage frequency in senile purpura patients. The control group received standard medications only. The study was open-label and not randomized.

7.3 Broader Khavinson peptide clinical evidence

The broader Khavinson peptide bioregulator program has produced clinical evidence across multiple organ systems, with the longest follow-up studies spanning 6 to 12 years [12, 13]. The Anisimov and Khavinson (2010) review in *Biogerontology* summarized results from multiple clinical applications, reporting that long-term peptide bioregulator treatment was associated with reduced mortality and improved functional status in elderly populations [12]. However, these studies were predominantly conducted at Russian research institutions, were generally open-label or observational in design, and have not been independently replicated by Western clinical trial programs.

7.4 Limitations of the clinical evidence

The clinical evidence for Vesugen is subject to several important limitations:

All studies were conducted at Russian research institutions, predominantly the Saint Petersburg Institute of Bioregulation and Gerontology and affiliated centers. No independent clinical trials have been conducted at institutions outside the Khavinson research network.

No randomized, double-blind, placebo-controlled trials of Vesugen have been published. The available studies are open-label, uncontrolled, or use historical comparison groups.

Sample sizes are small (32 to 49 patients). Statistical power for detection of moderate effect sizes is limited.

Clinical endpoints are heterogeneous and include biological age indicators, subjective health assessments, and surrogate markers (cholesterol levels, capillary strength) rather than hard cardiovascular outcomes (myocardial infarction, stroke, cardiovascular mortality).

Publication in Russian-language journals limits accessibility for international review and replication.

8. Sourcing and Quality Verification

Vesugen is available from multiple sources in different formulation categories:

Supplement-grade Vesugen: Capsule formulations containing lyophilized Vesugen are sold as dietary supplements in Russia and through international supplement distributors. The capsule typically contains 200 mcg of peptide complex. Quality control for supplement-grade material varies by manufacturer and jurisdiction; certificates of analysis may not include full peptide characterization.

Research-grade Vesugen: Multiple peptide research suppliers (Peptide Sciences, CosmicNootropic, Limitless Life Nootropics, ChemiNova, and others) supply synthetic Vesugen at stated purities of 98 to 99 percent by HPLC, typically in 20 mg or 50 mg vials as lyophilized powder. Research-grade material is accompanied by certificates of analysis including HPLC chromatograms and mass spectrometry confirmation of molecular weight.

Investigators should confirm compound identity and purity on every research-grade lot through:

- Reverse-phase HPLC with ultraviolet detection, confirming purity greater than 98 percent
- Electrospray ionization mass spectrometry confirming the expected $[M+H]^+$ at m/z 391.17
- Amino acid analysis confirming the Lys:Glu:Asp ratio of 1:1:1
- Residual solvent analysis and residual trifluoroacetic acid quantitation
- Endotoxin testing (limulus amoebocyte lysate assay) for material intended for cell culture or injectable research use

Third-party analytical verification is recommended, as the peptide bioregulator market includes preparations of variable quality, and the short chain length makes the compound susceptible to contamination with deletion sequences (dipeptide fragments) or with racemized material.

9. Reconstitution and Handling

Vesugen is supplied as a lyophilized powder (research-grade vials) or as capsules (supplement preparations).

Reconstitution for research use: Lyophilized Vesugen is reconstituted in sterile water for injection or in bacteriostatic water (0.9 percent benzyl alcohol preserved) to a stock concentration of 1 to 10 mg/mL. The peptide is freely soluble in aqueous media at neutral pH. For cell culture applications, reconstitution in phosphate-buffered saline (pH 7.4) or in serum-free cell culture medium is appropriate. The working concentration used in published cell culture studies is 200 ng/mL [5], though dose-response relationships have been characterized over a broader range.

Storage: Lyophilized powder should be stored at -20 degrees Celsius in a desiccated environment. Reconstituted solutions should be stored at 2 to 8 degrees Celsius and used within 14 to 30 days (consistent with bacteriostatic water stability standards). For longer storage of reconstituted material, aliquoting into single-use volumes and storage at -20 degrees Celsius is recommended. The peptide is expected to tolerate at least 5 freeze-thaw cycles without significant degradation, though single-use aliquoting is preferred.

Handling precautions: The compound is a standard research peptide with no unusual handling requirements. Standard laboratory personal protective equipment (gloves, laboratory coat, eye protection) is appropriate. The compound is not classified as hazardous under standard chemical safety frameworks at research concentrations.

Stability: The tripeptide bond between lysine and glutamic acid and between glutamic acid and aspartic acid is stable under normal storage conditions. Degradation pathways include hydrolysis (accelerated at extreme pH), deamidation of the aspartic acid side chain (slow at neutral pH), and racemization (negligible at storage temperatures). Stability-indicating analytical methods (RP-HPLC with comparison to reference standard) should be used to confirm integrity of stored material.

10. Stack Interactions and Combinations

Vesugen interacts with several compound classes through its proposed mechanisms and through the general pharmacology of its constituent amino acids:

Other Khavinson peptide bioregulators: Vesugen is frequently administered in combination with other peptide bioregulators in the Khavinson clinical paradigm. Common combinations include Vesugen with Pinealon (a brain-targeted tripeptide), Vesugen with Crystagen (an immune-targeted tripeptide), and Vesugen with Epitalon (a pineal gland-targeted tetrapeptide AEDG). The rationale is complementary tissue targeting. Additive or synergistic interactions between these peptides have not been formally characterized in controlled studies, though the Meshchaninov et al. (2015) study examined Vesugen and Pinealon in parallel [6].

Caloric restriction mimetics and SIRT1 activators: Vesugen's upregulation of SIRT1 expression suggests potential additive or synergistic interactions with other SIRT1-targeting compounds including resveratrol, nicotinamide mononucleotide (NMN), nicotinamide riboside (NR), and fisetin. The interaction has not been studied, but the convergent mechanism suggests pharmacological overlap.

Antihypertensive agents: Vesugen's normalization of endothelin-1 expression may produce additive effects with endothelin receptor antagonists (bosentan, ambrisentan, macitentan) and with other antihypertensive classes. The clinical significance of this interaction is unknown.

Statins and lipid-lowering agents: The Ventfort clinical study reported cholesterol reduction [7]. Concurrent administration with HMG-CoA reductase inhibitors (statins) may produce additive lipid-lowering effects, though this has not been studied.

Anticoagulants and antiplatelet agents: Vesugen's effects on endothelial cell function and connexin expression could theoretically modulate platelet-endothelial interactions. No bleeding or thrombotic adverse events have been reported, but concurrent use with anticoagulants warrants monitoring.

Nootropics and cognitive enhancers: The neuroprotective profile of Vesugen suggests potential combination with other cognitive compounds. No formal interaction studies have been conducted. The absence of receptor-mediated pharmacology (Vesugen does not target identified cell-surface receptors) reduces the likelihood of conventional pharmacodynamic interactions, though epigenetic interactions at the gene expression level are theoretically possible.

Proteolytic enzymes and enzyme supplements: Co-administration with oral protease supplements may accelerate gastrointestinal degradation of orally administered Vesugen, potentially reducing absorption. Separation of dosing by at least 30 minutes is a reasonable precaution.

11. Adverse Events and Safety

11.1 Reported safety profile

The safety profile of Vesugen in published studies is characterized by the absence of reported serious adverse events. The Meshchaninov et al. (2015) study in 32 patients reported no adverse events attributable to Vesugen [6]. The Kitachev et al. (2014) study in 41 patients reported no adverse events [11]. The Ventfort clinical study in 49 patients reported tolerability comparable to standard treatment with no serious adverse events [7]. The broader Khavinson peptide bioregulator program has reported a generally favorable safety profile across multiple preparations and across clinical follow-up periods of 6 to 12 years [12, 13].

The Meshchaninov et al. (2015) study noted decreased CD34+ hematopoietic cell counts during Vesugen treatment [6]. The clinical significance of this finding was not established, and the authors interpreted it as inhibited blood cell production unrelated to adaptive immune responses. This finding warrants monitoring in future studies, particularly with chronic administration.

Neither Vesugen nor Pinealon affected chromatin condensation in the Meshchaninov et al. study, which the authors interpreted as evidence of nuclear genetic safety [6].

11.2 Theoretical safety considerations

Genotoxicity: The proposed mechanism of DNA binding raises theoretical concerns about genotoxicity and mutagenesis. The available evidence (absence of chromatin condensation changes, absence of reported neoplastic outcomes) does not support a genotoxic signal, but formal genotoxicity testing (Ames test, micronucleus assay, chromosomal aberration assay) results have not been published for Vesugen specifically.

Immunogenicity: Tripeptides are below the molecular weight threshold (typically greater than 1000 Da) for immunogenicity. Allergic reactions to Vesugen are not expected and have not been reported.

Reproductive toxicity: No reproductive toxicity data are available. Use during pregnancy and lactation is not recommended in the absence of safety data.

Long-term safety: The absence of long-term controlled safety data is the principal safety limitation. The 6 to 12 year follow-up data from the broader Khavinson program are observational and do not constitute systematic pharmacovigilance.

11.3 Regulatory status

Vesugen is not approved as a pharmaceutical product by any national regulatory authority, including the Russian Ministry of Health, the United States Food and Drug Administration, the European Medicines Agency, or any other regulatory body. It is sold as a dietary supplement in some jurisdictions and as a research-grade peptide. The regulatory classification does not require demonstration of safety and efficacy to pharmaceutical standards.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative vaso-protective and geroprotective peptide compounds against Vesugen, evaluated on five standards: novelty, effect size, promising potential, side-effect profile, and overall validation. The comparators were selected to represent the principal peptide-based approaches to vascular aging, endothelial protection, and geroprotection that share mechanistic or clinical space with Vesugen.

12.1 Epitalon (AEDG; Ala-Glu-Asp-Gly)

Mechanism: Synthetic tetrapeptide bioregulator targeting the pineal gland. Epitalon stimulates melatonin production and telomerase activity. The compound is the synthetic analog of Epithalamin, a polypeptide complex extracted from bovine pineal gland tissue. Proposed mechanisms include telomere elongation through telomerase activation, antioxidant activity through melatonin upregulation, and regulation of neuroendocrine aging through hypothalamic-pituitary axis modulation [12, 17].

Novelty: Moderate. The telomerase activation mechanism is distinctive within the Khavinson peptide class and has attracted substantial attention in the longevity research community. The peptide sequence (AEDG) shares two of four residues (Glu, Asp) with the three residues of Vesugen (Lys, Glu, Asp), suggesting potential overlap in DNA binding preferences.

Effect size: Epitalon demonstrated statistically significant telomerase activation in human fetal fibroblast cultures and in human pulmonary fibroblast cultures, with extension of the proliferative lifespan of cells beyond the Hayflick limit in some reports [17]. In rodent studies, long-term Epithalamin/Epitalon treatment increased mean lifespan by approximately 25 percent. Effect sizes in human clinical studies are not reported in controlled trial format.

Promising potential: Moderate. Epitalon is the most widely studied Khavinson synthetic peptide and has the largest community of interest in the longevity research space. However, like Vesugen, it lacks regulatory approval and independent

replication.

Side-effect profile: No serious adverse events have been reported. The safety profile is similar to Vesugen: favorable in small studies with limited follow-up.

Overall validation: Moderate. The evidence base is larger than for Vesugen and includes published telomerase activity data, but remains predominantly from the Khavinson laboratory network.

Comparison to Vesugen: Epitalon targets neuroendocrine aging and telomere biology rather than vascular endothelial function. The two peptides are complementary rather than competitive and are frequently co-administered in the Khavinson clinical paradigm. Vesugen has the advantage of tissue-specific vascular targeting; Epitalon has the advantage of a more broadly studied mechanism (telomerase) with greater recognition in the international research community.

12.2 Thymalin (thymic peptide complex)

Mechanism: Polypeptide complex extracted from calf thymus gland. Thymalin restores immune function through modulation of T-cell maturation and function. It is one of the original Khavinson peptide bioregulators and has been registered as a pharmaceutical product in Russia for immunodeficiency states [12, 13].

Novelty: Low. Thymic peptide extracts for immune modulation are a well-established therapeutic category with multiple commercial preparations worldwide (thymosin alpha-1, thymopentin, thymulin).

Effect size: In a landmark 15-year clinical follow-up study, combined Thymalin and Epithalamin treatment of elderly patients was associated with significantly reduced mortality compared to untreated controls [12]. In shorter-term studies, Thymalin improved immune markers (T-cell counts, natural killer cell activity) in immunocompromised elderly patients.

Promising potential: Moderate. Thymalin has registered pharmaceutical status in Russia, giving it an operational advantage over unregistered preparations.

Side-effect profile: Favorable. Decades of use in Russian clinical practice have not identified serious adverse events. Allergic reactions are rare.

Overall validation: Moderate to high within the Russian pharmacological framework. The 15-year mortality data are the strongest long-term outcome data in the Khavinson peptide program, though they remain from a single research center.

Comparison to Vesugen: Thymalin targets immune function rather than vascular endothelial biology. The two compounds are frequently co-administered for systemic geroprotection. Thymalin has the advantage of registered pharmaceutical status and longer clinical experience; Vesugen has the advantage of tissue-specific vascular targeting.

12.3 Liraglutide (GLP-1 receptor agonist)

Mechanism: Synthetic analog of glucagon-like peptide-1 (GLP-1) with acylation for albumin binding and extended half-life. Liraglutide is a 31-amino-acid peptide approved for type 2 diabetes and obesity. Cardiovascular protection has been demonstrated in the LEADER trial (9,340 patients), with significant reduction in major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke) [18]. The cardiovascular mechanism involves endothelial protection, anti-inflammatory effects, and direct cardioprotection through GLP-1 receptor activation on cardiomyocytes and endothelial cells.

Novelty: High in the context of cardiovascular protection by a metabolic peptide. The GLP-1 receptor agonist class represents a paradigm shift in cardiovascular risk reduction.

Effect size: Large. The LEADER trial demonstrated a 13 percent reduction in the composite cardiovascular endpoint (hazard ratio 0.87, 95 percent confidence interval 0.78 to 0.97) and a 22 percent reduction in cardiovascular mortality [18]. These are hard cardiovascular outcomes in a large, multicenter, randomized, double-blind, placebo-controlled trial.

Promising potential: Very high. Liraglutide and the broader GLP-1 receptor agonist class (semaglutide, tirzepatide) are in active global development and registration for cardiovascular, metabolic, and neurodegenerative indications.

Side-effect profile: Well characterized. Gastrointestinal adverse events (nausea, vomiting, diarrhea) are common (20 to 40 percent) and dose-dependent. Pancreatitis risk is elevated. Thyroid C-cell tumors have been observed in rodents but not confirmed in humans. The benefit-risk profile is well established and supports regulatory approval.

Overall validation: Very high. The evidence base includes multiple Phase 3 cardiovascular outcome trials with thousands of patients and long-term follow-up.

Comparison to Vesugen: Liraglutide and Vesugen share the broad category of peptide-based cardiovascular protection but differ fundamentally in mechanism (receptor-mediated versus proposed epigenetic), in evidence base (Phase 3 cardiovascular outcome trials versus small open-label studies), in regulatory status (globally approved versus unregulated), and in molecular class (31-amino-acid acylated peptide versus unmodified tripeptide). Liraglutide is the standard-of-care peptide for cardiovascular protection; Vesugen is an early-stage research compound. The comparison illustrates the gap between the Vesugen evidence base and the standard required for clinical validation of cardiovascular protection claims.

12.4 BPC-157 (Body Protection Compound)

Mechanism: Pentadecapeptide (15 amino acids) derived from human gastric juice protein. BPC-157 has demonstrated vasoprotective, wound-healing, and anti-inflammatory effects in extensive preclinical studies, including promotion of angiogenesis, modulation of nitric oxide system activity, and protection against endothelial damage in multiple organ systems [19]. The compound interacts with multiple molecular targets including the nitric oxide system, prostaglandin system, and dopaminergic pathways.

Novelty: Moderate. The gastroprotective peptide concept is established; BPC-157's extension to systemic vascular and tissue-protective applications is more novel.

Effect size: Substantial in preclinical models across multiple organ systems (gastrointestinal, cardiovascular, musculoskeletal, neurological). Animal studies demonstrate consistent wound-healing acceleration, angiogenesis promotion, and tissue protection. Human clinical data are limited to a small number of studies.

Promising potential: Moderate. BPC-157 has a large preclinical evidence base and widespread research use but limited clinical development. Like Vesugen, it lacks regulatory approval for any indication.

Side-effect profile: Preclinical studies report no significant toxicity. Human safety data are limited.

Overall validation: Low to moderate. Extensive preclinical data but limited clinical validation. The evidence base is broader and more internationally diverse than Vesugen's.

Comparison to Vesugen: BPC-157 and Vesugen share the category of peptide-based vasoprotective compounds without regulatory approval. BPC-157 has a substantially larger preclinical evidence base, more diverse tissue-protective applications, and a larger international research community. Vesugen has the advantage of a more specific proposed molecular mechanism (epigenetic regulation through DNA binding) and more specific tissue targeting (vascular endothelium). Neither compound has adequate clinical validation for therapeutic claims.

12.5 Semax (Met-Glu-His-Phe-Pro-Gly-Pro)

Mechanism: Synthetic heptapeptide analog of ACTH(4-10), developed in Russia and registered as a pharmaceutical product for cognitive and cerebrovascular indications. Semax modulates brain-derived neurotrophic factor (BDNF) expression, dopaminergic and serotonergic neurotransmission, and cerebral blood flow [20]. The compound has demonstrated neuroprotective and nootropic activity in clinical studies of stroke recovery, cognitive impairment, and optic nerve disease.

Novelty: Moderate. The ACTH fragment approach to neuroprotection is established; Semax represents a specific optimization within this class.

Effect size: Moderate in clinical studies of stroke recovery and cognitive impairment. Semax has demonstrated improvement in neurological deficit scores and cognitive measures in controlled clinical trials conducted at Russian research centers [20].

Promising potential: Moderate. Semax has registered pharmaceutical status in Russia and a clinical evidence base that, while predominantly Russian, is more developed than Vesugen's.

Side-effect profile: Favorable. Administered intranasally. No serious adverse events reported in clinical use spanning over two decades in Russia.

Overall validation: Moderate. Registered pharmaceutical with clinical trial data, though predominantly from Russian research centers.

Comparison to Vesugen: Semax and Vesugen share the category of Russian-developed peptide bioregulators with neuroprotective and vascular indications. Semax has the advantages of registered pharmaceutical status, a receptor-mediated mechanism (ACTH/melanocortin receptor pathway), a larger clinical evidence base, and demonstrated cerebrovascular protection in stroke patients. Vesugen has the advantage of a more specific vascular endothelial targeting mechanism and a distinct (epigenetic) proposed mechanism of action. For purely vascular research applications, Vesugen is more specifically targeted; for cerebrovascular and cognitive applications, Semax has stronger clinical validation.

12.6 Comparator summary

The five comparator compounds span a spectrum from globally approved cardiovascular therapeutics (liraglutide) to Russian-registered pharmaceuticals (Thymalin, Semax) to unregulated research peptides (Epitalon, BPC-157). Vesugen occupies the least validated position on this spectrum, with the smallest clinical evidence base and the most preliminary mechanistic characterization. Its principal distinguishing features are the ultrashort tripeptide structure, the proposed epigenetic mechanism through DNA promoter binding, the specific vascular endothelial targeting, and the integration into the broader Khavinson peptide bioregulator paradigm with its emphasis on tissue-specific peptide regulation of aging.

The practical research positioning of Vesugen is as a tool compound for investigation of short-peptide-mediated epigenetic regulation of vascular endothelial aging, rather than as a validated therapeutic agent for cardiovascular disease. Investigators considering Vesugen should calibrate expectations against the liraglutide evidence standard (Phase 3 cardiovascular outcome trials) and should recognize the substantial gap between the current Vesugen evidence base and the validation required for therapeutic claims.

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